Rare SOX2+ Airway Progenitor Cells Generate KRT5+ Cells that Repopulate Damaged Alveolar Parenchyma following Influenza Virus Infection.

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Public Summary:
Influenza virus has the potential to cause life-threatening lung disease and long-term structural remodeling of lung tissue. We sought to determine the cellular dynamics of lung repair following influenza infection and define the identity and source of epithelial progenitor cells that repair and repopulate injured airway and gas-exchange regions of the lung. We found that virus-induced airway injury elicited the expansion of airway basal stem cells that repair airways and colonize damaged alveoli in a mouse model. Repopulation of injured airway and alveolar regions lead to proximalization of distal airways by pseudostratified epithelium and of alveoli by airway-derived epithelial cells that lack the normal characteristics of mature airway or alveolar epithelium. These studies shed new light on mechanisms of lung tissue remodeling following severe influenza virus infection.

Scientific Abstract:
Recent studies have implicated keratin 5 (KRT5)+ cells in repopulation of damaged lung tissue following severe H1N1 influenza virus infection. However, the origins of the cells repopulating the injured alveolar region remain controversial. We sought to determine the cellular dynamics of lung repair following influenza infection and define whether nascent KRT5+ cells repopulating alveolar epithelium were derived from pre-existing alveolar or airway progenitor cells. We found that the wound-healing response begins with proliferation of SOX2+ SCGB1A1- KRT5- progenitor cells in airways. These cells generate nascent KRT5+ cells as an early response to airway injury and yield progeny that colonize damaged alveolar parenchyma. Moreover, we show that local alveolar progenitors do not contribute to nascent KRT5+ cells after injury. Repopulation of injured airway and alveolar regions leads to proximalization of distal airways by pseudostratified epithelium and of alveoli by airway-derived epithelial cells that lack the normal characteristics of mature airway or alveolar epithelium.